REMARKS

Claims 1 and 3-18 are pending, claims 5, 6, 11, and 14-16 are withdrawn, and claims 1, 3, 4, 7-10, 12, 13, 17, and 18 are under consideration. In an Office Action mailed June 23, 2008, the Examiner entered Applicants' submission filed on April 16, 2008 and withdrew the finality of the previous Office Action in response to Applicants' request for continued examination. On Page 2, the Examiner omitted claims 12 and 13 from the list of considered claims. The Examiner withdrew rejections under 35 U.S.C. §103 in view of Applicants' prior response. The Examiner rejected claims 1, 3, 4, 7-10, 17, and 18 under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the enablement requirement. The Examiner also rejected claims 1, 4, 7, 8, 10, 12, 17, and 18 under 35 U.S.C. §102 for alleged anticipation by US Patent No. 6,146,888 to Smith *et al.* (the Examiner inadvertently duplicated the number "10"). The Examiner also rejected claims 1, 3, 4, 7-10, 12, 13, 17, and 18 under 35 U.S.C. §103(a) for alleged obviousness over Smith *et al.* in view of West *et al.* (US Patent Application Publication No. 2004/0219563). In light of the amendments and for the reasons noted below, Applicants respectfully request reconsideration.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1, 3, 4, 7-10, 17, and 18 for encompassing methods that are allegedly not enabled. While conventional methods require cells to be electroporated in a buffer, Applicants teach electroporation in a culture medium. Paragraph [0026] provides support for the amendments. Without intending to be limited as to the theory of the invention, components in the medium are believed to alter electroporation conditions such that the conditions distinguish the recited method from others, including those non-enabled methods described by Benvenisty and discussed in Applicants' prior response and the most recent Office Action. Further, Applicants add new claims 19-21 to recite additional electrical conditions suitable for electroporating human ES cells. Applicants respectfully request reconsideration.

Rejection under 35 U.S.C. §102 and 35 U.S.C. §103(a)

The Examiner rejected claims 1, 4, 7, 8, 10, 12, 17, and 18 as being anticipated by Smith. Smith does not anticipate the amended claims because Smith does not teach or suggest electroporation of human ES cells in a culture medium. Smith discloses electroporation of murine ES cells in phosphate buffered saline (col. 7, line 19-38).

Even if Smith suggested the use of medium, Smith cannot constitute an enabling disclosure of homologous recombination into human pluripotent stem cells because neither the properties nor the culturing conditions of such human cells were known as of Smith's filing. Smith allegedly embraces all animal cells, especially of mammalian species, including human cells. However, Smith's filing date predates the isolation and public disclosure of human embryonic stem cells. Even if human embryonic stem cells had been known at Smith's filing, the intervening public knowledge of human embryonic stem cell culture cannot simply be combined with the Smith disclosure because the methods then known for targeting homologous recombination by electroporation were non-enabling in human embryonic stem cells, as has been acknowledged by Benvenisty.

The Examiner also combined Smith with West et al. that is said to teach inserting DNA markers into human genes by homologous recombination. Notwithstanding the teachings in West, Smith is essential to the Examiner's rejection. However, for the reasons noted above, Smith does not disclose, teach or suggest performing the electroporation method in culture medium, and, likewise, does not employ electrical conditions as recited in the newly presented claims. As Applicants and the Examiner have noted throughout prosecution of this application, suitable conditions for electroporation of hESC were not readily apparent to the skilled person and were not made apparent by Smith. Even in the face of this difficulty, Applicants were the first to disclose suitable conditions in their patent application. Without Smith, West cannot stand alone as a basis for rejecting the claims. Applicants respectfully request reconsideration.

Amendments to Claims 12 and 13

Applicants here amend Claims 12 and 13 to ensure clarity. The amended claims clarify that in cells purified as in Claim 7 and its dependents one can identify expressed genes that are characteristic of the cells. One can then purify from a culture that contains differentiated cells a population of cells expressing those genes. While the methods of Claim 12 can yield purified cells expressing genes characteristic of a particular lineage of differentiated cells, the purified cells can also be undifferentiated cells, as is exemplified in Claim 13, where, on the basis of characteristic expression of the recited genes, undifferentiated cells can be purified from a culture that contains differentiated cells.

Support for the amendment is provided in paragraph [00010] which provides that "[b]ecause the method permits the purification of cells of defined lineages, it then becomes possible to characterize the molecular markers of cells of that lineage and to use those markers to purify cells of that lineage from other mixed populations of cells." Paragraph [00035] also states that "The availability of the first purified cultures of successor lineages of differentiated cells from ES cells makes possible the development of techniques to generally screen cell populations to make other similar cultures. The first purified cultures created as described here will be transgenic for the inserted genetic construct and it is desirable to create similar purified populations of progeny cells derived from ES cell cultures which are not transgenic. This is done as follows. *After the first purified population of cells of the specific lineage is created, cells of that culture are subjected to a profiling step to characterize several cellular markers specific to cells of that lineage. This can be done any number of ways, but the most efficient ways currently for doing this are by cDNA microarray gene expression analysis and by serial analysis of gene expression (SAGE). The results of that analysis will be the identification of sets of genes which are characteristic of cells that have committed to that specific lineage. With the information about that set of genes in hand, it then becomes possible to select from those genes one or more genes (and preferably three or four genes) which express cell surface markers. The expression of those cell surface markers can then be used as a test for differentiation to the lineage. New non-transgenic cultures of ES cells can be permitted to differentiate, with or without bias toward the desired progeny lineage. Then the cell surface markers can be used to screen from the mixture of cells to purify the cells that have differentiated into the desired lineage. Thus the creation of purified populations of cells of desired progeny lineages is generally enabled by the methods described here, whether or not the cells have a genetic construct inserted in them.*" (emphasis added).

The method is also generally contemplated in the Lineage Purification section of the Specification between paragraphs 29 and 32. Paragraph 32 provides particular support for Claim 13, where the purified cells of defined lineage express markers of undifferentiated cells. This is described as being a useful way to maintain a culture of undifferentiated cells.

Consideration of these amendments are respectfully requested.

Fees

A Petition for an extension of time for three months accompanies this response so the response will be deemed to have been timely filed. If any other extension is due in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee due to Deposit Account No. 17-0055. No other fee is believed due, but if any other fee is due in this or any subsequent response, please consider this to be a request to charge the fee to the same Deposit Account.

Respectfully submitted,

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